

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference ON/4-33683A	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. PCT/EP2005/002756	International filing date (day/month/year) 15.03.2005	Priority date (day/month/year) 16.03.2004
International Patent Classification (IPC) or national classification and IPC C07D405/04, C07D417/06, C07D493/04, A61K31/427, A61P35/00		
Applicant NOVARTIS AG		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
 - a. ☐ sent to the applicant and to the International Bureau a total of sheets, as follows:
 - ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
 - ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
 - b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand 12.12.2005	Date of completion of this report 13.02.2006
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Seelmann, I Telephone No. +49 89 2399-



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2005/002756

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-57 as originally filed

Claims, Numbers

1-9 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 1 (part), 2 (part), 3, 4-9 (part), 8 (industrial applicability)

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 1 (part), 2 (part), 3, 4-9 (part)
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form

- ☐ has not been furnished
- ☐ does not comply with the standard

- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
- ☐ restricted the claims.
 - ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☒ neither restricted nor paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1,2, 4-9 (all part) .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1,2,4-9
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1,2,4-9
Industrial applicability (IA)	Yes: Claims	1,2,4-7,9
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Prior art:

- D1: US-B1-6 441 186
- D2: ANGEWANDTE CHEMIE. INT. ED., vol. 36, no. 19, 1997, pages 2097-2103
- D3: WO 99/28324 A
- D4: WO 00/37473 A
- D5: TETRAHEDRON, vol. 58, no. 32, 5 August 2002, pages 6413-6432

Re Item III

Claim 8 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV

The common structural feature of the compounds according to claim 1 of the present application is represented by formula I. This unit is, however, known from the documents D1 to D5 (cf. compounds and generic formula cited in the search report), which are considered as the closest state of the art for the present application. The compounds of D1-D5 possess the same qualitative activity as those of the application.

D1-D3 and D5 disclose compounds which correspond to compounds of the present application with R1=a), D4 discloses compounds with R1=b). A single general inventive concept (Rule 13(1) PCT) between the different compounds is thus not detectable. This single inventive concept is defined as "involving one or more of the same or corresponding special technical features" (Rule 13(2) PCT), which serve to distinguish the current application from the prior art (establishes novelty) and are responsible for the inventive activity.

However, the compounds with R1=a) still lack a single general inventive concept vis-a-vis D1-D3 and D5. D1 and D2 disclose compounds which correspond to compounds of the present application with R1=a), Z=bond (D1, compound 42; D2, compound 109,110) and

Z=O (D1, compound 38; D2, compound 107) and R2=H, therefore, the compounds with Z=O, C and "bond" form separate inventions. Moreover, the compounds with Z=O and Z=bond are still not unitary vis-a-vis D1 and D2, (additionally the compounds with Z=bond are still not unitary vis-a-vis D3). Compounds 38 and 42 of D1 have R2=H, the compounds with R2=H and R2=alkyl also form separate inventions. Furthermore, compounds with R1=b) still lack a single general inventive concept vis-a-vis D4. The compounds of Example 51 and 52 of D4 correspond to compounds of the present application with R1=b), Z=bond (compound 51) and Z=O (compound 52) and R2=Me and R3=H (additionally compounds 17 and 18 show R3=OH), therefore, the compounds with Z=O, C and "bond" form separate inventions. Again the compounds with Z=O and Z=bond are still not unitary vis-a-vis D4, because compounds 51 and 52 have R2=Me and R3=H and compounds 17 and 18 have R2=Me and R3=OH. The compounds with R2=H and R2=alkyl and the compounds with R3=H and R3=OH also form separate inventions.

Re Item V

1. NOVELTY

The subject-matter of the claims is considered to be novel (Article 33(2) PCT). The essential structural difference between the claimed compounds and those of D1 and D2 resides in the R2 substituent. R2 is alkyl in the first invention of the present application, but H in D1 (compound 42) and D2 (compound 107). D3 differs in the definition of Z, it is Z=O in the first invention of the present application, but Z is a bond in D3 (Example 4). D4 differs in the nature of the R1 substituent. D5 differs in R3, which is H in the first invention of the present application, but OH in D5 (compound 2).

2. INVENTIVE STEP

The subject-matter of the claims does not fulfil the requirements of Article 33(3) PCT.

The closest state of the art for the present application is represented by D1-D5. They disclose similar epothilone derivatives having anti cancer activity which do not fall under the present application because of the structural differences as outlined above, only. In the present application, such a structural variation is alleged to lead to alternative derivatives

with the same qualitative activity as those described in D1-D5. In view of the experimental part and the other information as given in the description, it can be assumed that this problem has been solved for the claimed compounds. The problem underlying the present application can, however, not be seen in the provision of further novel derivatives, because the proposed solution would be seen as obvious. In view of the extremely close structural relationship to the compounds of D1-D5 it is considered that the man skilled in the art would regard the new compounds of this application as being obvious alternatives to the known compounds. Especially because in the present case each of the substituents, which distinguishes the claimed compounds from one prior art is known from another, as various combinations of the substituents are already known in the art, it is obvious for the man skilled in the art to try further combinations. The compounds of the present application appear to contain no structural feature which would make them inventive per se.

Therefore, the problem underlying the present application should be seen in the provision of new derivatives having unexpected properties over those of the closest prior art compounds (D1-D5). In the absence of comparative test results or other appropriate information it is not possible to decide whether such a problem has been solved or not.

It should be noted that the term "lower alkyl" is unclear and does not fulfill the requirements of Article 6 PCT. It could be changed in the sense of page 4.